Clinical Efficacy of Short Contact Topical 5-Fluorouracil in the Treatment of Keratoacanthomas

A Retrospective Analysis

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ABSTRACT

Objective: To determine the efficacy of treating patients with a recent onset, biopsy-proven keratoacanthoma with short-contact topical 5% 5-fluorouracil cream twice daily until resolution. **Design:** Chart review of 10 patients who applied 5% 5-fluorouracil for the treatment of biopsy-proven keratoacanthoma. **Setting:** Outpatient clinic of a board-certified dermatologist. **Participants:** The study population was 90-percent women (9/10), 10-percent men (1/10) and ranged in ages from 52 to 92 years old with a mean age of 74.4. **Measurements:** Patients were followed for weekly visits for the duration of their treatment and at varying, less-frequent intervals after resolution of the lesion clinically. Photographs were taken at each visit. **Results:** The authors performed a retrospective analysis of 10 patients with biopsy-confirmed keratoacanthomas treated with topical 5-fluorouracil. One patient elected to have Mohs surgery after one week of topical 5-fluorouracil due to personal concern and cosmetic appearance and did not complain of any side effects due to the drug. Of the nine patients that remained on topical 5-fluorouracil, all patients had complete resolution of the lesion within six weeks. The range in the number of weeks to resolution was four to six weeks. Two patients required a one- to two-week drug holiday secondary to erythema, which resolved without any further complication or patient discomfort. All nine patients who continued therapy reported satisfaction with the results and showed excellent compliance with treatment. **Conclusion:** Short-contact topical 5% 5-fluorouracil appears to provide excellent cosmetic results and is well-tolerated by patients. This should be an initial consideration for the treatment of keratoacanthomas and does not preclude future surgical intervention if deemed necessary. (*J Clin Aesthet Dermatol.* 2014;7(11):35–37.)

Keratoacanthomas (KAs) are generally regarded as self-healing, squamous cell tumors without the ability to metastasize. These unsightly lesions typically spontaneously regress over time, usually within a few months. However, because of the disfiguring and troublesome cosmetic appearance of these lesions, the potential pain associated with the lesions, and the potential for rapid enlargement, as well as local destruction from expansion, patients will often undergo surgery to have the lesions removed.[1,2]

The major nonsurgical therapies for the treatment of KAs can be divided into local and systemic therapies. Local therapies are composed primarily of intralesional injections and topical therapies. However, other methods, such as electrodessication and curettage and laser therapy have been reported.[1,2] The ideal agent would speed resolution and provide a superior cosmetic result. 5-fluorouracil (5-FU) has shown promise in the treatment of KAs in various routes—intralesional injection, topically, and combined with laser.[1,3] In order to further investigate topical treatment of KAs, the authors performed a chart review of patients with biopsy-confirmed KAs that were managed with topical 5-FU.

PATIENTS

The authors reviewed the charts of all patients diagnosed with KAs in the private and university dermatology practice of a board-certified dermatologist. They then selected all KAs that were biopsy proven. Within these cases, only the

DISCLOSURE: The authors report no relevant conflicts of interest.
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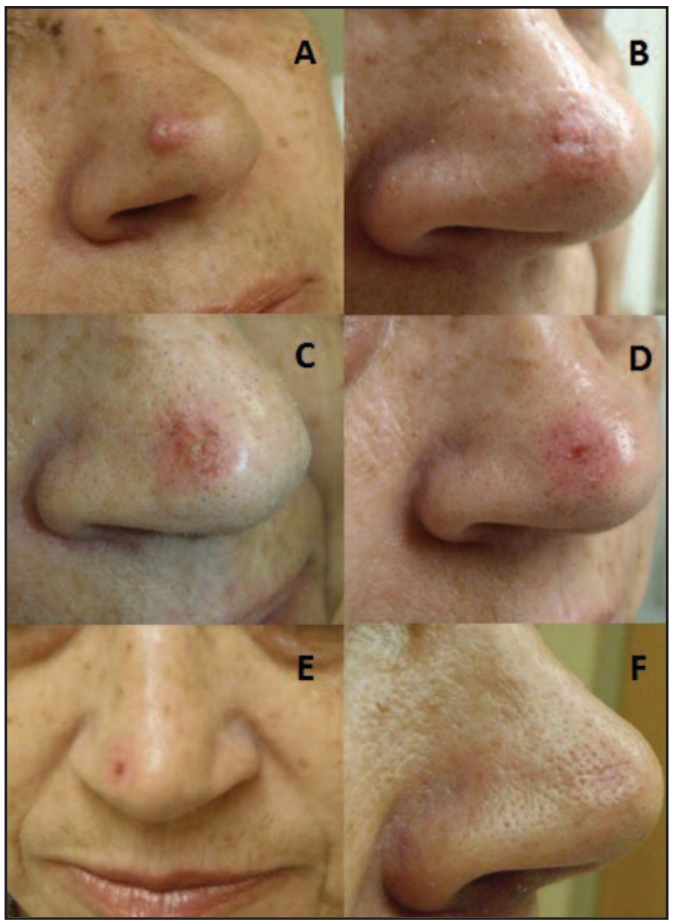

Figure 1. Patient at initial presentation with 0.8cm pink, firm papule with central keratin plug. 5% topical 5-fluorouracil prescribed and therapy begins, Day 0 (A); Patient at one-week follow-up after applying BID topical 5-FU, showing flattening of lesion and mild surrounding erythema, Day 7 (B); Continued therapy, Day 14 (C); Crusting almost entirely resolved and central erosion with surrounding mild-to-moderate erythema noted, Day 21 (D); Healing central erosion and mild erythema present and no palpable textural change or firmness on exam—last day of therapy, Day 28 (E); Patient four months after therapy completed (F).

patients having been treated with topical 5-FU in a standardized fashion were included. The method of application in all patients was to apply the topical 5-FU to the lesion while taking caution to avoid the surrounding normal skin as possible. Tape or an adhesive bandage was then placed over the lesion and the 5-FU allowed to remain under occlusion for one hour. After one hour, the tape was removed and the area was gently wiped clean as necessary to remove any remaining cream. This was done twice daily until resolution of the lesion. The endpoint was determined clinically by the physician when the lesion was no longer palpable and no visual evidence of persistence of the lesion existed. Minimal erythema may be present. In some cases if resolution was not clear, a biopsy was performed to confirm resolution.

RESULTS

In the authors' series of 10 patients, each patient had a solitary KA in a sun-exposed area. Five of the lesions were on the lower extremities and five were on the face (Figure 1). Unfortunately, the sizes of the lesions were not uniformly documented upon chart review; however, photos were available from baseline and from each weekly visit for each patient. In all nine cases that continued treatment with 5-FU, complete resolution was noted after four to six weeks of therapy. Only Patients 2 and 5 required a two-week and one-week period off medication, respectively. This was due to mild local erythema at the site of 5-FU application. In both instances, the erythema resolved. In Patient 2, after the resolution of the erythema and irritation, the lesion appeared clinically resolved and 5-FU was not restarted. In Patient 5, erythema had resolved after one week and 5-FU was re-initiated due to clinical persistence of the lesion. The patient completed four weeks of treatment with 5-FU with complete resolution of the KA.

DISCUSSION

Although KAs are spontaneously resolving lesions that do not require treatment, patient anxiety combined with physician concern for enlargement of the lesion that could result in localized destruction often leads to intervention.[1] 5-FU has shown great promise in various routes—intralesional injection, topically, and combined with laser.[1] Treatment of KAs with local 5-FU was first described in 1962 by Klein et al and has since been used in dermatological practices as a staple for almost 50 years.[1,2] The mechanism of action of 5-FU is thus well-understood. Through ribosylation and phosphorylation, 5-FU binds thymidylate synthetase by way of cofactor 5, 10 methyl-enetetrahydrofolate. This results in the inhibition of thymidylate synthetase, leading to the eventual depletion of thymidine and finally, the reduced synthesis of deoxyribonucleic acid (DNA).[1,2,4]

5-FU is not readily taken up by normal skin, but penetration of the abnormal skin (lesional) and minimally the normal perilesional skin does occur.[2,4] Systemic side effects have not been reported, likely due to the minimal systemic uptake, thus making for a desirable safety profile.[1,5] Side effects that have been reported in relation to topical application of 5-FU include local inflammation, burning, serous oozing, and allergy.[5] Many of these are more appropriately described as manifestations of the desired effect in a technical sense when one considers that 5-FU-mediated necrosis of lesional cells is the end goal. However, the irritation may exceed the level of comfort of either or both the patient or physician and warrant decreased concentration and/or frequency (or cessation).[5] Despite this, the treatment appears to be well-tolerated by patients in both the literature and within the authors' series.[1–3,5,6]

The fact that topical 5-FU is taken up primarily by the abnormal cells that are rapidly growing within the KA with little effect on surrounding normal skin, together with the careful application of the cream by our patients, is likely

responsible for the mild side effects reported by patients receiving this therapy.[2,4] Two of the authors' nine patients exhibited mild erythema at the site of topical 5-FU application for which therapy was held for 1 to 2 weeks for the erythema to resolve.

Topical 5-FU has proven to be an effective treatment option for large KAs and those in particular locations making surgery or other therapies less favorable, such as the concha of the ear and the nasal wall. One potential limiting factor of using topical 5-FU as the initial therapy for KAs is that it may not be as effective in treating KAs that are not rapidly proliferating. However, in the authors' review, they found that all lesions responded to therapy, although one patient chose to abort therapy and undergo surgery.

SUMMARY

Short-contact topical 5-FU therapy appears to provide excellent cosmetic results and is well-tolerated by patients. The range in time to resolution of the lesion in the auhors' patients was 4 to 6 weeks. The most commonly reported side effects reported were mild irritation and erythema. One patient required a week cessation from the medication before restarting and another experienced erythema and irritation at the end of her treatment.

Since surgical intervention will lead to scarring, nonsurgical options should first be considered. Nonsurgical methods would not preclude any future surgical intervention, so this can always be considered should noninvasive therapy fail or progress too slowly. Following the patient with a sound treatment plan is key. It is important for the physician and patient to continually assess the progress of treatment since determination must be made as to whether or not the current treatment is effective and when to alter the treatment plan and consider additional therapeutic options.

The primary goal of treatment in patients with KAs should be to prevent enlargement that may lead to damage and destruction by local expansion. Therapy should at least slow or prevent enlargement of the lesion and ideally would accelerate the time to resolution. Based on our results and similar results found in the literature, an initial consideration for the treatment of KAs should be topical 5-FU, particularly those in which surgical intervention is likely to lead to morbidity and disfigurement. This is supported by the excellent patient compliance, satisfaction, and cosmetic result found with use of topical 5-FU for the treatment of KA.

The major limitations of this study were small size, retrospective analysis, and that the natural history of KAs is to spontaneously involute. The retrospective nature of the study introduces both selection and recall bias. However, this study as well as the case reports and small case series in the existing literature serve to underscore the need for further investigation of this treatment modality, particularly as randomized placebo-controlled trials.

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